REMARKS

Claims 1-41 are in this application. Claims 1-9 have been examined. Claims 10-41 are withdrawn. The species election of Ca^{2+} is affirmed.

Claim 1 has been amended to include the subject matter of original claim 2. Claim 2 has been cancelled.

According to the Official Action, claims 1-9 are rejected as being anticipated under 35 USC 102(a) by Tsuda et al. (Nature, 14 August 2003, vol. 424, p. 778-783). This rejection is respectfully traversed.

To be a bar under 35 USC 102(a), the alleged anticipation must be the act of someone other than the inventor of the application in question.

Attached are the declarations of Akito Mizokoshi, Michael W. Salter and Yukari Shigemoto-Mogami in which these authors declare that they have reviewed the specification and claims of this application and they are not inventors of the subject matter claimed in this application. Therefore, since the remaining named authors are named as inventors of this application, the Tsuda reference is not citable as a reference as it is the inventors' own publication which was published less than one year prior to the filing date of this application.

Therefore, it is respectfully requested that the rejection be withdrawn.

According to the Official Action, claims 1 and 3-9 are rejected as being anticipated under 35 USC 102(b) as being anticipated by Lynch et. al. (US Patent 6,242,216). This rejection is respectfully traversed.

Claim 2 is not included in this rejection. Claim 1 has been amended to include the subject matter of claim 2 and claim 2 has been cancelled.

Therefore, it is respectfully requested that the rejection be withdrawn.

According to the Official Action, claims 1-9 are rejected under 35 USC 103(a) as being unpatentable over Wood et al. (Pharmacological Characterisation of the Human P2X4 Receptor Using FLIPR, Pharmacology Reviews and Communications, vol. 10, p. 341-347) in view of Tsuda et al. (Mechanical Allodynia Caused by Intraplantar Injection of P2X Receptor Agonist in Rats: Involvement of Heteromeric $P2X_{2/3}$ Receptor Signaling in Capsaicin-Insensitive Primary Afferent Neurons, Journal of Neuroscience, 2000, vol. 20, p. RC90/1-RC90/5). This rejection is respectfully traversed.

As stated in the Action by the Examiner, Wood et al. do not teach that the method of claim 1 can be used to identify compounds useful in the treatment of neuropathic pain, in particular, tactile allodynia induced after nerve injury.

Accordingly, the claimed invention is different from Wood et al. in that a compound inhibiting an interaction of a P2X4 receptor agonist and P2X4 receptor on a surface of a cell is identified as useful for the treatment or prevention of tactile allodynia induced after nerve injury (step (c)). This feature of the present invention cannot be established without a finding that the action of P2X4 receptor induces tactile allodynia after nerve injury.

The Examiner believes that Tsuda et al. teach the above technical feature of the present invention.

As indicated in the Action on page 20, the second paragraph, Tsuda et al. state, in particular, that "It has been postulated that ATP and P2X receptors play a role in various pain states," and that "...the mechanisms underlying P2X receptor-mediated mechanical allodynia may be one of the determining factors of the mechanical allodynia in these painful states. Elucidation of this pathway may lead to the discovery of a new class of compounds that suppress mechanical allodynia in pathological pain."

The Examiner believes that the above disclosure in Tsuda et al. teach a relationship between P2X receptors and pain. However, Tsuda et al. do not teach the above technical feature of the present invention for reasons as set forth below.

P2X receptors are known to consist of seven subtypes, i.e. P2X1, P2X2, P2X3, P2X4, P2X5, P2X6, and P2X7. In addition, some of these subtypes are known to be combined to form heteromer-channel receptors having various functions different from those of original single subtypes. Please find enclosed herewith a copy of Gonzalo E. Torres et al., Hetero-oligomeric Assembly of P2X Receptor Subunits. J. Biological Chemistry 274, 6653-6659, 1999. This document explains this fact. P2X receptor which has been known at the time the present invention was made includes 18 receptors, such as P2X1, P2X2, P2X3, P2X4, P2X5, P2X6, P2X7, P2X1+2, P2X1+3, P2X1+5, P2X1+6, P2X2+3, P2X2+5, P2X2+6, P2X3+5, P2X4+5, P2X4+6, and P2X5+6.

In addition, pain includes broadly various types of disorder which are induced by different causes, for example, usual pain due to tissue damage, allodynia, anesthesia dolorosa, causalgia, central pain, hyperalgesia, hyperpathia, and the like. Among them, allodynia includes various types of disorder.

Therefore, a person of ordinary skill in the art would not have had a reasonable expectation of success in selecting a combination of P2X4 receptor and tactile allodynia induced after nerve injury from wide variety of P2X receptors and painful disorders in reference to disclosure by Tsuda et al.

In particular, mechanical allodynia researched by Tsuda et al. is essentially different from tactile allodynia induced after nerve injury to be treated in the claimed invention. The mechanical allodynia of Tsuda et al. is acute allodynia which is introduced by injection of ATP agonist into

skin and continues for about an hour. This type of allodynia does not involve injury of any neurocytes. In contrast, the tactile allodynia to be treated in the claimed invention is chronic allodynia which is introduced by injury of neurocytes and continues for several days to several years.

Therefore, Tsuda et al. do not teach that P2X4 receptor is involved in tactile allodynia induced after nerve injury, although they state that the mechanisms underlying P2X receptor-mediated mechanical allodynia may be one of the determining factors of "the mechanical allodynia" in these painful states.

Further, P2X4 receptor has been indicated to be associated with other disorder than pain. For example, please find enclosed a copy of a paper in Neuroscience, which suggests that P2X4 receptor is indicated to be associated with hippocampal damage after ischemia (page 96, left column, lines 6-8 of Cavaliere, F. et al., 2003, Up-regulation of P2X2, P2X4 Receptor and Ischemic Cell Death: Prevention by P2 Antagonists. Neuroscience 120(1), 85-98). Therefore, P2X4 receptor could not be directly associated with pain, in particular, the tactile allodynia in reference to Tsuda et al.

The standard test used to establish *prima facie* obviousness is the test set out by the Supreme Court in *Graham v. John Deere* (383 US 1, 148 USPQ 459 (1966)). To determine whether a claim is *prima facie* obvious:

1) the scope and content of the prior art are to be determined;

2) the differences between the prior art and the claims at issue are to be ascertained; and

3) the level of ordinary skill in the pertinent art resolved.

In addition, according to MPEP 2141, citing *Hodosh v. Block Drug Co., Inc.,*

786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n. 5 (Fed. Cir. 1986), when applying 35 USC 103, the following tenets of patent law must be adhered to:

1) the claimed invention must be considered as a whole;

2) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; and

3) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention.

Considering the claimed invention and the references as a whole, it is clear that there is not suggestion of the invention of a method of identifying a compound useful for the treatment or prevention of tactile allodynia induced after nerve injury, comprising:

(a) contacting a cell expressing $P2X_4$ receptor on the surface thereof, with a test compound, in the presence of $P2X_4$ receptor agonist,

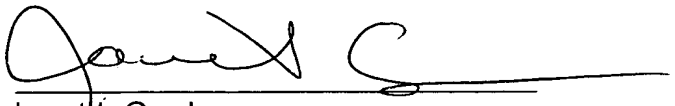
(b) determining whether or not said test compound inhibits an interaction of said $P2X_4$ receptor agonist and $P2X_4$ receptor on the surface of the cell, and

(c) identifying the test compound which inhibits said interaction, as useful for the treatment or prevention of tactile allodynia induced after nerve injury .

Accordingly, the claimed method is not obvious over Wood et al. in view of Tsuda et al. and it is respectfully requested that the rejection be withdrawn.

It is submitted that the application is in condition for allowance and favorable consideration is respectfully requested.

Respectfully submitted,



Janet I. Cord
c/o Ladas & Parry LLP
26 West 61st Street
New York, NY 10023
Reg. No. 33,778 (212) 708-1935